REMARKS

Claims 1-6 and 21-25 have been canceled without prejudice for re-presentation in a continuing application. Claims 7-20 remain pending in the application along with new claims 26-36.

Claims 7, 9, 13, 15, 17, and 19 have been revised to correct clerical errors and to recite the inherent feature of HIF-1 inhibition as necessary. No change in claim scope is intended or believed Claim 8 has also been revised to correct a clerical error.

Support for new claim 26 is found in the specification at least at page 15, third full paragraph. Support for new claims 27 and 28 is found at least on page 15, fourth full paragraph, of the instant specification.

No new matter has been introduced, and no new issue requiring further search and/or consideration is present. Entry of the above revised claims is respectfully requested.

Alleged rejection under 35 U.S.C. §112, first paragraph

1) Claims 7-20 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly enabled only for the inhibition of tumor growth with the mannose YC-1 derivative because the specification is asserted as failing to enable "inhibiting HIF-1 expression, inhibiting angiogenesis in tumor cells or tissues, inhibiting tumor progression and metastasis, treating a HIF-1-mediated disorder or condition by all polyol YC-1 derivatives claimed." Applicants have carefully reviewed the statement of the rejection as well as the rejection as presented in the previous Office Action mailed March 24, 2006 and respectfully traverse because no *prima facie* case of non-enablement is present. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Before addressing this rejection in detail, Applicants point out that the claimed subject matter is based in part upon the recognition that compounds of Formula I, with and without the polyol moiety at position R_1, targets HIF-1 in cancer cells. This is summarized at pages 3-4, bridging paragraph, and supported throughout the specification and figures, including the working examples, which includes demonstration of *in vivo* effectiveness for YC-1 mannose in Example 10. The ability to target HIF-1 allows the possible application of the compounds to treat tumor cells and tumor cell related angiogenesis as disclosed and encompassed by the

pending claims. Applicants respectfully submit that no factual evidence has been presented to cast doubt upon the above.

Turning to the rejection, Applicants point out the well established standard that an application must be taken as presumptively enabling unless there is objective reason to doubt the statements contained therein (see MPEP 2164.04 and the case decisions cited therein, such as *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). This presumption means that the burden of the *prima facie* case is on the Office to provide objective reasons why enablement is not present. Therefore, it is improper to shift the burden to Applicants to prove the presence of enablement. Based upon this standard, Applicants submit that no objective reason has been provided to doubt the presumption of enablement in the pending claims, and that the instant rejection improperly attempts to shift the burden to Applicants to prove the presence of enablement.

The instant rejection is based in part upon cited documents by Lee et al. (J. Med. Chem., 2001) and Yeo et al. (J. Natl. Can. Inst., 2003) as allegedly supporting the view that "[t]esting one polyol with one test such as tumor growth does not provide substantial evidence that all the polyol derivatives will be effective" (see page 4 of the Office Action mailed March 24, 2006). Applicants respectfully submit that this position is misplaced because a) the cited documents do not negatively impact the presumption of enablement in the instant application, and b) the statement appears to improperly require additional "tests" with other compounds to establish the presence of enablement.

With respect to a), Applicants point out that the assertion of Lee et al. reporting that '[o]ut of all the derivatives synthesized and tested it was concluded that only five of the indazole compounds showed promise as antiplatelet candidates out of about 31 compounds" is immaterial to the instantly claimed subject matter. Lee et al.'s report is unrelated to the inhibition of HIF-1 and the treatment of tumors or tumor related angiogenesis because there is no indication that antiplatelet activity is co-extensive with HIF-1 inhibition. Therefore, it is only speculation that Lee et al.'s screens for antiplatelet activity raise doubts regarding the HIF-1 inhibiting activity of the derivatives featured in the pending claims.

As for Yeo et al., their report on YC-1 as a potential anticancer agent via the targeting of HIF-1 supports the presumption of enablement in the instant case because the claimed subject matter is very closely related to YC-1. In fact, the compounds featured in the pending claims

differ from the family of YC-1 compounds only by the presence of a single polyol moiety at one end of the molecule. There is no evidence that the presence of such a moiety has any negative effect on the HIF-1 inhibiting ability of the compounds. To the contrary, Example 10 and Figure 16 of the instant application clearly demonstrate that the presence of a representative polyol moiety on the compounds did not remove the HIF-1-mediated antitumor activity.

Given the presence of these consistent facts, Applicants respectfully submit that it is improper for the Office to require additional "tests" (see b) above) or "a representative set of the polyol derivatives encompassed by the claims" (see page 3, first full paragraph, Office Action mailed December 19, 2006) because there has been no objective reason provided to cast doubt on the presence of enablement. The lack of an objective reason is further seen in the assertion that "it cannot be assume[d] just because one derivative exhibits like behavior as YC-1, that all the derivatives will exhibit the same behavior" (see page 3, first full paragraph, Office Action mailed December 19, 2006). No objective reason is given for why the "assumption" cannot be made. The statement of the instant rejection also fails to recognize that the skilled person in the field would appreciate that the structure-function relationship of the base Formula I compounds to HIF-1 inhibitory activity leads to an expectation that the presence of a small moiety on one end of the compounds would not negatively affect their HIF-1 inhibiting activity.

Finally, Applicants point out that the ultimate determination is whether undue experimentation is needed to make and use the claimed invention. It is well settled that the presence of enabled subject matter does not mean the presence of complete predictability or the lack of experimentation. To the contrary, the absence of complete predictability is clearly permitted, and the presence of routine and/or repetitive experimentation is the opposite of undue experimentation. These standards are evident from the facts of *In re Wands*, where the screening for additional monoclonal antibodies, without the presence of complete predictability as to their presence or form but with the use of routine and repetitive experimentation, was held as enabled. Applicants respectfully submit that the instant case is analogous to the situation in *Wands* because there is an expectation that additional compounds modified only by the addition of an R_1 polyol moiety would retain the same anti-HIF-1 activity, and so the level of unpredictability is acceptable. Moreover, no more than routine and/or repetitive experimentation is needed to screen additional tumor cells for the expression of HIF-1, indicating that they would be

susceptible to the compounds of Formula I, and to confirm the HIF-1 inhibitory activity of the compounds encompassed by Formula I.

In light of the foregoing, Applicants respectfully submit that this rejection is misplaced and may be properly withdrawn.

2) Claims 7-20 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly enabled only for the inhibition of tumor growth with the mannose YC-1 derivative because the specification is asserted as failing to enable "inhibiting HIF-1α expression in tumor cells or tissues, inhibiting tumor growth, inhibiting HIF-1-regulated gene expression, inhibiting angiogenesis in tumor cells or tissues, inhibiting tumor progression and metastasis, treating a HIF-1-mediated disorder or condition for all cancers by all polyol YC-1 derivatives claimed." Applicants have carefully reviewed the statement of the rejection as well as the rejection as presented in the previous Office Action mailed March 24, 2006 and respectfully traverse because no *prima facie* case of non-enablement is present. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Background information regarding the claimed subject matter and the presumption of enablement has been presented above. The instant rejection is based in part upon the position that "no one drug that can broadly treat cancer" (see page 6 of the Office Action mailed March 24, 2006). Applicants submit that they do not disagree with the assertion, but respectfully point out that the claimed subject matter is not directed to the treatment of all cancers without limit. To the contrary, the claims feature the targeting of HIF-1 as present in tumor cells. There is no objective reason given as to why the targeting of HIF-1 in tumor cells would require undue experimentation.

Instead, the rejection (on page 7 of the Office Action mailed March 24, 2006) relies upon a news article regarding the drug endostatin where endostatin is structurally unrelated to Formula I and is immaterial with respect to HIF-1 inhibition. The rejection also relies upon a 1997 document by Gura to suggest that model systems for discovery of anti-cancer drugs are not predictive. But there is only the rejection's assertion that use of the model systems requires undue experimentation. Applicants respectfully submit that no more than routine and repetitive experimentation is needed, especially where the model systems are used to screen drug compounds of a defined structure, such as those of Formula I, and where there is already

evidence of efficacy in an *in vivo* model and knowledge of the targeted molecule (HIF-1) as important for tumor angiogenesis and tumor survival.

As explained above, the presence of enabled subject matter does not require absolute predictability or the absence of experimentation. Like the rejection addressed above, there is an expectation in the instant case that additional compounds modified only by the addition of an R_1 polyol moiety would retain the same HIF-1 targeting activity. Therefore, the level of unpredictability is acceptable. Moreover, no more than routine and/or repetitive experimentation is needed to screen additional tumor cells for the expression of HIF-1, indicating that they would be susceptible to the compounds of Formula I, and to confirm the HIF-1 inhibitory activity of the compounds encompassed by Formula I.

In light of the foregoing, Applicants respectfully submit that this rejection is misplaced and may be properly withdrawn.

2) Claims 19-20 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly enabled only for the treatment of hepatoma with the mannose YC-1 derivative because the specification is asserted as failing to enable "treatment of all HIF-1-mediated disorder or conditions in a mammal with all polyol YC-1 derivatives." Applicants have carefully reviewed the statement of the rejection as well as the rejection as presented in the previous Office Action mailed March 24, 2006 and respectfully traverse because no *prima facie* case of non-enablement is present. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Background information regarding the claimed subject matter and the presumption of enablement has been presented above. The instant rejection is very similar to that addressed immediately above with respect to "no one drug that can broadly treat cancer" (see page 10 of the Office Action mailed March 24, 2006 for the assertion in the instant rejection). Again, Applicants submit that they do not disagree with the assertion, but respectfully point out that the claimed subject matter is not directed to the treatment of all cancers without limit. To the contrary, claims 19 and 20 feature the targeting of HIF-1 as it is present in mammals with an HIF-1-mediated disorder. There is no objective reason given as to why the targeting of HIF-1 in mammalian cells would require undue experimentation.

Instead, this rejection (on pages 10-11 of the Office Action mailed March 24, 2006) relies upon the same news article regarding the drug endostatin where endostatin is structurally

unrelated to Formula I and is immaterial with respect to HIF-1 inhibition. This rejection also relies upon the 1997 document by Gura to suggest that model systems for discovery of anti-cancer drugs are not predictive. But there is only the rejection's assertion that use of the model systems requires undue experimentation. The statement of the instant rejection fails to explain why use of the model system is equivalent to undue experimentation, especially where so many skilled practitioners in the field continue to use those very same model systems on a daily basis. Moreover, there is no object reason given as to why these articles are relevant to the inhibition of HIF-1 in a mammal or predictive of results with the use of Formula I compounds.

Applicants respectfully submit that like the situation discussed above, no more than routine and repetitive experimentation is needed. This is especially clear where knowledge regarding HIF-1 is high and includes the ability to determine HIF-1 expression and activity in cells of a mammal. As explained above, the presence of enabled subject matter does not require absolute predictability or the absence of experimentation. Like the rejection addressed above, there is an expectation in the instant case that additional compounds modified only by the addition of an R_1 polyol moiety would result in the retention of the HIF-1 inhibiting activity. Therefore, the level of unpredictability is acceptable. Moreover, no more than routine and/or repetitive experimentation is needed to screen mammals with an HIF-1-mediated disorder or condition for the effectiveness of the compounds of Formula I in inhibiting HIF-1.

In light of the foregoing, Applicants respectfully submit that this rejection is misplaced and may be properly withdrawn.

Alleged rejection under 35 U.S.C. §112, second paragraph

Claims 19-20 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting "HIF-1-mediated disorder or condition" without "specifically point[ing] out if the disorder is mediated positively or negatively." Applicants have carefully reviewed the statement of the rejection as well as the rejection as presented in the previous Office Action mailed March 24, 2006 and respectfully traverse because no *prima facie* case of indefiniteness is present. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

As an initial matter, Applicants traverse the characterization of claims 19 and 20 as "omnibus claims." The definition of "omnibus claim" is present at MPEP 2173.05(r) and does not encompass claims 19 and 20.

Applicants further point out that individual terms in a claim are not to be read in a vacuum but rather in the context of the overall claim. Claim 19 has been revised to include the inherent feature of inhibiting HIF-1 by application of Formula I compounds. Therefore, the supposed question of whether the HIF-1-mediated disorder or condition is mediated positively or negatively by HIF-1 is misplaced because the claims are directed to the broad scope of inhibiting HIF-1 in such a disorder or condition regardless of how HIF-1 mediates the disorder.

Applicants respectfully remind the Office that as set forth at MPEP 2143.04 and the case decisions cited therein, "[b]readth of a claim is not be equated with indefiniteness." Therefore, this rejection is misplaced and may be properly withdrawn.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR §§ 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

JHK Law

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